Kindly add new claim 23, as follows:

23. (New) The method of claim 2, wherein said cognitive dysfunction is selected from the group consisting of memory deficit, amnesia, impaired spatial/non-spatial stimulus association, senility, and dementia.

REMARKS

After entry of the present amendments, claims 2, 5-11, and 23 are pending. Claims 1, 3-4, and 12-22 are cancelled without any prejudice to prosecute the subject matter of these claims in a later application. New claim 23 is drawn to a specific embodiment of the present invention. Support for this amendment is found in the specification at p. 4, lines 1-10; p. 5, lines 1-12; and p. 15, lines 3-5. Claim 2 has been amended to recite that the method is drawn to protecting against cognitive dysfunction or reducing memory dysfunction associated with hippocampal tissue damage, and that the morphogen is selected from a specific enumerated group of well-known, well-characterized morphogens. Claim 2 has further been amended to recite the dosage of morphogen administered. Claims 5, and 7-11 have been amended to reflect proper dependency, and to clarify the subject matter claimed. Support for these amendments is found in the specification, as originally filed, at p. 2, lines 11-27; p. 5, lines 5-9; p. 16, line 15 to p. 18, line 16; and p. 39, lines 7-10. These amendments do not introduce new matter.

Applicant respectfully requests that the correction of any defects in the drawings be deferred until the present application is allowed.

RESTRICTION REQUIREMENT

Applicant confirms the election of Group I, claims 1-22, made on June 8, 1999.

INFORMATION DISCLOSURE OBJECTION

The Examiner alleges that the listing of references in the specification is not a proper information disclosure statement, and that any references not cited by the Examiner on Form

PTO-892 have not been considered.

Applicant's previous representatives filed an Information Disclosure Statement, Form PTO-1449, and copies of the cited references in the present case on January 23, 1998. Applicant encloses herewith a copy of that IDS and Form PTO-1449, as well as a copy of the "Received" return postcard acknowledging the receipt of these documents. Applicant will resubmit copies of the cited references if the Examiner so requires. Applicant respectfully requests that the Examiner consider and make these documents of record, as evidenced by the signing and return of the enclosed Form PTO-1449.

§112, FIRST PARAGRAPH, ENABLEMENT REJECTIONS

The Examiner has rejected claims 1-22 under 35 U.S.C. §112, first paragraph, as lacking enablement. The Examiner alleges, *inter alia*, that undue experimentation is required to practice the claimed methods because: (a) the skilled artisan does not know "when, or if, they have successfully practiced the instant invention"; (b) it is unclear what "what constitutes a therapeutically effective amount" of morphogen; (c) "neurons do not regenerate in the CNS," hence *in vivo* methods of treatment are unpredictable; (d) the skilled artisan cannot "extrapolate what critical amino acids constitute the tissue-specific morphogenic function"; (e) the stimulation of an N-CAM or L1 isoform by "*non neuronal tumorigenic* cells *in vitro* provides no nexus for extrapolating to effective *in vivo* treatment"; and (f) insufficient guidance is provided to administer morphogen to the CNS (September 2, 1999, Office Action at p. 6-10). Applicant traverses.

Claims 1, 3-4, and 12-22 have been cancelled. Accordingly, the rejection of these claims is now moot. Claim 2, as amended, addresses the Examiner's rejections.

First, claim 2, as amended, recites a method for protecting against cognitive dysfunction or reducing memory dysfunction by administering a specifically recited morphogen, selected from an enumerated group of well-known, well-characterized morphogens, administered at a dose of between 0.01 to 100 mg/kg of body weight of the mammal per day.

Accordingly, upon administration of one of the specifically recited morphogens, in the specifically recited dose according to the claimed method, the skilled artisan will be crystal clear that they have successfully practiced the instant invention.

Second, as noted above, claim 2, as amended recites a particular dose. Further, the claims, as amended, recite specific dosages for administration. Specifically, the claims recite that the morphogen is administered at a dose of between 0.01 to 100 mg/kg of body weight of the mammal per day. Support for this amendment is found in the specification at p. 39, lines 7-16. Accordingly, claim 2 (and its dependent claims) make clear the dosage that constitutes a therapeutically effective amount. Further, the "therapeutically effective amount" language no longer appears in the pending claims.

Third, it is beyond question that the specifically recited morphogens are capable of inducing tissue-specific morphogenesis in mammals. *See, e.g.*, p. 16, line 15 to p. 18, line 16; p. 2, lines 11-27.

In particular, the specification teaches that administration of morphogen protects and/or repairs cognitive function in a mammal and reduces memory dysfunction, including memory deficits, amnesia, and/or impaired spatial or non-spatial stimulus associations (*see, e.g.*, p. 4, lines 1-10). The specification also teaches that such dysfunction is associated with hippocampal tissue damage and/or medial temporal lobe damage (*see, e.g.*, p. 5, lines 5-9).

Further, the specification teaches that morphogen administration protects, restores, and repairs memory function in mammals affected by neuronal cell loss resulting, *e.g.*, from aging (*see*, p. 5, lines 17-22), and that morphogen administration maintains the neural pathway via the growth and maintenance of differentiated neurons, and is useful in treatment of neural disorders characterized by reduced or lost cellular metabolic function (*see, e.g.*, p. 14, line 27 p. 15, line 7). The specification also provides an example of morphogen-induced hippocampal dendrite morphogenesis and synapse formation (*see* part IV(C), p. 59-61).

Finally, the specification also teaches *in vivo* models for hippocampal tissue damage, including the art-accepted model of forced ischemic episode or stroke (*see* Examples 7-10, p. 45-48, *citing, e.g.*, Gotti *et al.*, *Brain Res. 522:* 290-307 (1990)). Similarly, several behavior

models for assessing cognitive function are provided in the specification (*see* part IV, including Examples 11-15, p. 48-55).

All that is required for enablement is that one skilled in the art be able to *practice* the *claimed* invention, given the level of knowledge and skill in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (CA FC 1991). It is not necessary to show an expectation of success. Here, the specification does enable the skilled artisan to practice the claimed invention without undue experimentation. *See Hybritech Inc. v. Monoclonal Antibodies, Inc* , 802 F.2d 1367, 1384 (CA FC 1986), *cert. denied*, 107 S.Ct. 1606 (1987); MPEP § 2164.01.

For these reasons, the Examiner's rejection on the ground that the "neurons do not regenerate in the CNS," is not relevant to these claims as amended.

Fourth, as noted above, the claims as amended, recite specific well known morphogens, with reference to specific SEQ ID Nos. Accordingly, the morphogens recited in the claims are are structurally defined. Support for these amendments is found throughout the specification, *e.g.* at p. 62-72; p. 11, line 23 to p. 12, line 15; p. 18, lines 17-24; p. 39, lines 7-12. For this reason, the Examiner's rejection that the skilled artisan cannot "extrapolate what critical amino acids constitute the tissue-specific morphogenic function" has been overcome.

Fifth, claims 2, and 5-11, as amended, no longer recite stimulation of N-CAM or L1 isoforms as a functional limitation of the morphogen. This rejection is moot.

Sixth, the specification provides sufficient guidance for administration of the specifically morphogen to the CNS in the claimed methods. In particular, the specification teaches that morphogen may be administered in a number of ways including, *e.g.* intraventricularly, and intracisternally, directly to the CNS (*see* p. 39, line 17 to p. 40, line 21, *citing* REMINGTON'S PHARMACEUTICAL SCIENCES (1990); Examples 1-3, p. 41-43). Further, the specification also specifically provides for well known modifications and formulations useful to enhance morphogen administration across the blood-brain barrier, including truncation, conjugation to carrier molecules, or alteration of lipophilicity (*see, e.g.*, Pardridge, *Endocrine Reviews 7*:

314-330 (1986); United States patent 4,801,575; Kastin *et al.*, *Pharmac. Biochem. Behav. 11:* 713-16 (1979)).

§112, SECOND PARAGRAPH, REJECTIONS

The Examiner has rejected claims 15-22 under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner alleges that the recitation of "% identity or % homology" renders the claims indefinite, and that the recitation of "N-CAM or L1" isoform is an ambiguous functional limitation (September 2, 1999, Office Action at p. 17-18).

Applicant has cancelled claims 15-22 in order to expedite prosecution and allowance of the present application. Accordingly, this rejection is moot, and should be withdrawn.

§102 REJECTIONS

The Examiner has rejected claims 3-7 and 9-10 under 35 U.S.C. §102(b), as being anticipated by The Regents of the University of California/Harland *et al.* (WO 95/06656 (1995); "*Harland*"). The Examiner alleges that *Harland* disclose methods of treating conditions characterized by necrosis or loss of neurons by administering the morphogen, dor3, "thereby encompassing and meeting all limitations" of the claims (September 2, 1999 Office Action at p. 18-19). Applicant traverses.

Harland fails to disclose each and every limitation of the present claims, and thus cannot anticipate. *See* MPEP §2131, *citing Verdegaal Bros. V. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (CA FC 1987). The claims, as amended, recite that the morphogen useful in the claimed methods is selected from an enumerated group of well-known, well-characterized morphogens. These morphogens are capable of inducing tissue-specific morphogenesis in mammals. *See, e.g.*, p. 16, line 15 to p. 18, line 16; p. 2, lines 11-27. *Harland's* dor3 is not among the enumerated morphogens, nor does *Harland* teach the physiologic aspects underlying neurodegenerative disorders that can be affected by dor3 administration, nor how cognitive function can be assessed. This rejection should be withdrawn.

The Examiner has also rejected claims 1-10 and 19 under 35 U.S.C. §102(b), as being anticipated by Wang *et al.* (WO 95/05846 (1995); "*Wang*"). The Examiner alleges that *Wang* disclose methods of treating a mammal "having a neural defect, neural damage or a neural condition" by administering a morphogenic protein, hence the "disclosure of Wang encompasses all limitations" of the present claims (September 2, 1999, Office Action at p. 19). Applicant respectfully traverses.

Wang does not contemplate administration of morphogen to treat ***cognitive*** disorders, nor provides any guidance on how cognitive function can be assessed. Rather, *Wang* disclose the stimulation of ***astrocytes*** by administration of BMP. As the "Background" section of *Wang* notes, astrocytes are ***not*** neurons, but rather function in axonal guidance and stimulation of neurite outgrowth. Hence, *Wang* does not, and cannot, address protection against dysfunction associated with hippocampal tissue damage, as recited in the pending claims.

The claims are novel over *Wang*. The rejection should be withdrawn.

CONCLUSION

In view of the foregoing amendments, the pending claims are in condition for allowance.

If there are any questions, the Examiner is encouraged to contact the undersigned.

Respectfully submitted,

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